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Severe COPD Alters Muscle Fiber Conduction Velocity During Knee Extensors Fatiguing Contraction

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ABSTRACT

The aim of this study was to assess the changes in muscle fiber conduction velocity (CV), as a sign of fatigue during knee extensor contraction in patients with chronic obstructive pulmonary disease (COPD) as compared with healthy controls. Eleven male patients (5 with severe and 6 with moderate COPD; age 67 ± 5 years) and 11 age-matched healthy male controls (age 65 ± 4 years) volunteered for the study. CV was obtained by multichannel surface electromyography (EMG) from the vastus lateralis (VL) and medialis (VM) of the quadriceps muscle during isometric, 30-second duration knee extension at 70% of maximal voluntary contraction. The decline in CV in both the VL and VM was steeper in the severe COPD patients than in healthy controls (for VL: severe COPD vs. controls $-0.45 \pm 0.07\%/s$; $p < 0.001$, and for VM: severe COPD vs. controls $-0.54 \pm 0.09\%/s$, $p < 0.001$). No difference in CV decline was found between the moderate COPD patients and the healthy controls. These findings suggest that severe COPD may impair muscle functions, leading to greater muscular fatigue, as expressed by CV changes. The results may be due to a greater involvement of anaerobic metabolism and a shift towards fatigable type II fibers in the muscle composition of the severe COPD patients.

KEYWORDS

Electromyography; isometric contraction; neuromuscular fatigue; power spectral frequency; vastus lateralis; vastus medialis

Abbreviations

6-MWT	6-minute walk test
BMI	Body mass index
BODE	Body mass index, airflow obstruction, dyspnea and exercise capacity
CV	Muscle fiber conduction velocity
EMG	Electromyography
FEV	Forced expiratory volume
FEV ₁	Forced expiratory volume in 1 second
GOLD	Global Initiative for COPD
MNF	Mean power spectral frequency
VL	Vastus lateralis
VM	Vastus medialis

Introduction

Skeletal muscle dysfunction is a well-recognized extra-pulmonary manifestation of chronic obstructive pulmonary disease (COPD). Intrinsic muscular alterations, such as redistribution of fiber type ratio towards type II fibers (1) and reduction in muscle oxidative capacity (2), seem to be the main exercise-limiting factors in COPD patients (3), resulting in a significant reduction in endurance performance (2). The reduction in endurance capacity has been found to be correlated with disease stage (4–6). Recent studies have shown that leg muscle fatigability is strictly connected with daily physical activity and

that it predicts mortality, morbidity, and quality of life better than lung function measures (7).

Many physiological changes occur during fatiguing muscle contraction, including altered metabolic milieu (such as accumulation of hydrogen ions) (8), changes in muscle fiber conduction velocity (CV) (9), and alterations in the number and firing rate of the recruited motor units (10). The changes in surface electromyography (EMG) signals that occur during prolonged muscle contraction has been defined as EMG manifestation of fatigue. Decreases in CV and mean power spectral frequency (MNF) are typical EMG trends seen during fatiguing contraction (11) and they occur before mechanical task failure (12). Because greater recruitment of type II muscle fibers has been demonstrated to generate greater EMG manifestations of fatigue, measured as a higher rate of changes in EMG variables over time (13,14), multi-channel surface EMG has been proposed as a tool for the non-invasive characterization of muscle fiber composition (15). CV has been shown to be a more reliable and sensitive index of fatigue than power spectral frequency, which is usually adopted (16, 17). Moreover, the rate of change in CV is related to the decrease in muscle fiber pH during a sustained contraction (18).

In addition to conventional outcome measures of fatigue, such as mechanical task failure and decreased force capability after sustained contractions (16), monitoring EMG changes may yield useful insight in muscle fatigability muscle abnormalities in COPD patients. In our previous study we found that CV

changes during fatigue correlate to disease stage and endurance capacities in mild to very severe COPD patients (6). The aim of the present study was to investigate whether the changes in CV, as a sign of fatigue, during knee extensors contraction differ between patients with moderate and severe COPD, and healthy controls. We hypothesized that the rate of CV changes would be greater in the COPD patients than the healthy controls and that severe stage disease could be related to a steeper decline in CV than moderate stage disease.

Methods

Participants

Eleven men with a diagnosis of severe ($n = 5$) and moderate ($n = 6$) airflow obstruction were recruited for the study. Diagnostic criteria for chronic airflow obstruction were based on the GOLD document (19), for which the threshold is a post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) < 0.7 . The patients were categorized in GOLD stages according to the severity of airflow limitation: moderate (stage 2, FEV_1 50–80% of predicted) and severe (stage 3, FEV_1 30–50% of predicted). Eleven healthy matched-age males made up the control group. Table 1 presents the characteristics of the two groups.

All participants were clinically stable, without exacerbation of disease in the 4 weeks prior to the beginning of the study. Exclusion criteria were: respiratory tract infections; another respiratory disorder; major comorbidity (e.g., cardiovascular diseases, diabetes, cancer); lower limb joint diseases. All participants provided written informed consent before participation in the experiments. The study was approved by the Ethics Committee of the Department of Neurological and Movement Science, University of Verona, and carried out in accordance with the Declaration of Helsinki.

Procedure

In this experimental, cross-sectional study, two separate testing sessions were conducted. During the first session, pulmonary function and exercise tolerance were evaluated; during the second session (3 days later), surface EMG signals were recorded during isometric knee extensor contractions. Participants were instructed to refrain from strenuous physical activity during the 24 hours before each experimental session.

First session: FEV_1 and FVC were measured according to the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force methods (20) using a pulmonary function test instrument (Quark, Cosmed, Rome, Italy). Exercise tolerance was investigated with the 6-minute walk test (6MWT) according to a standardized protocol (21). Subjects were instructed to walk on a 30 m shuttle hallway at their own pace, while attempting to cover as much ground as possible in the allotted 6 minutes.

Second session: knee extensor isometric peak torque was measured using an isokinetic dynamometer (Cybex Norm, Ronkonkoma, NY, USA). Subjects were seated upright on the dynamometer chair and secured with a seatbelt. First the subjects were familiarized with the device by performing 10

submaximal isometric contractions at 60 degrees of knee extension (0 = full extension). Then maximal voluntary contraction (MVC) was obtained from the knee extensors in order to calculate the load level that would be used during surface EMG measurements. The MVC contractions were performed twice, with 5-minutes rest in-between; the angle of contraction was 60 degrees and the duration was 5 seconds. If the two MVCs differed by more than 5%, a third MVC was performed. During the MVC measurements, the subjects received visual feedback on exerted torque and strong verbal encouragement to reach the maximum level on each trial.

The highest MVC value was taken to calculate submaximal loads. Five minutes after the last MVC, the subjects performed a fatiguing submaximal position task. They were instructed to maintain a constant knee extension at 60 degrees until voluntary exhaustion (limited to 30 s), while supporting a load applied by the dynamometer equivalent to the 70% of MVC. They received visual feedback on a display about the actual knee angle and were instructed to hold the target value of 60 degrees. The task was considered failed when the limb moved ± 5 degrees for more than 3 seconds. Standardized encouragement to maintain the limb as stable as possible, was provided by an operator.

EMG recording

EMG signals were recorded from the vastus lateralis (VL) and vastus medialis (VM) muscles of the dominant leg in a single differential configuration using linear adhesive electrode arrays composed of eight electrodes (silver bars, 5×1 mm in size, 5 mm inter-electrode distance, OT Bioelettronica, Turin, Italy). The skin was slightly abraded with abrasive paste and cleaned with water in accordance with SENIAM recommendations for skin preparation (22) before placement of the electrode arrays. Optimal position and orientation of the array was sought for each muscle by visual inspection of the EMG signals.

The sites with clear muscle fiber action potential propagation and the main innervation zones were identified using a dry linear array of 16 electrodes with 5 mm inter-electrode distance (OT Bioelettronica). The adhesive electrode arrays were then placed parallel to the muscle fibers and distally with respect to the innervation zone, where unidirectional propagation of the motor unit action potentials was detected. To ensure proper electrode-skin contact, the electrode cavities of the arrays were filled with 20–30 μ L of conductive paste (Spes-Medica, Battipaglia, Italy). The electrode arrays were fixed with an extensible dressing (Fixomull®, Beiersdorf, Hamburg, Germany). The EMG signals were amplified, sampled at 2048 Hz, bandpass filtered (3-dB bandwidth, 20–450 Hz, 12 dB/oct slope on each side), and converted to digital data with a 12-bit A/D converter (EMG-USB, OT Bioelettronica). Samples were visualized during acquisition and then stored on a personal computer using OT BioLab software version 1.8 (OT Bioelettronica,) for further analysis. On completion of EMG measurement, subcutaneous tissue layer thickness was measured with an ultrasound scanner (Acuson P50, 7.5 MHz linear array transducer, Siemens, Germany) in the location where the adhesive arrays were positioned.

The EMG signals were visually inspected to select the best channels for estimating variables. The MNF and CV of the EMG signals were computed off-line with numerical algorithms (12)

Table 1. Means (\pm standard deviation) of groups' characteristics, lung function, and exercise tolerance values are reported.

Participants	N°	AGE (years)	BMI (kg/m ²)	FEV ₁ (% of predicted)	FEV ₁ /FVC (% of predicted)	BODE	6MWT (m)
Healthy	11	66 \pm 5	26.8 \pm 2.9	114.4 \pm 19.5	103 \pm 5	1.0 \pm 0.0	653 \pm 80
COPD	11	67 \pm 5	28.1 \pm 4.2	59.2 \pm 19.2	57 \pm 13	2.4 \pm 0.7	441 \pm 107
Moderate	6	67 \pm 5	29.3 \pm 3.3	67.7 \pm 9.0**	62 \pm 7**	2.3 \pm 0.5**	493 \pm 54**
Severe	5	68 \pm 5	25.4 \pm 2.5	39.0 \pm 7.6**§§	45 \pm 15**§§	3.0 \pm 0.5**§§	342 \pm 74**§§

6-minute walk test (6-MWT); Body mass index (BMI); Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE); Forced vital capacity (FVC); Forced expiratory volume in 1 second (FEV₁); Statistically significant differences of severe COPD compared to healthy subjects are reported:

** $p < 0.01$, and compared to moderate COPD are reported as §§ $p < 0.01$.

using non-overlapping signal epochs of 0.5 seconds. The average CV was estimated among all the accepted channels and computed as e/d , where e is the inter-electrode distance and d is the delay time between the signals obtained from the two double differential arrays spaced 5 mm apart. The correlation coefficient between the two adjacent double differential signals was calculated; if the correlation coefficient was < 0.8 , the recorded signals were excluded from the analysis. MNF estimates were averaged from the accepted channels.

Statistical analysis

Linear regression analysis was applied to the time course of the EMG variables since it has been demonstrated to be the best model to fit EMG data acquired during fatiguing contractions (11). The initial value of each EMG variable was calculated as the intercept of the regression line at time = 0 s, which is the first instant of muscle contraction where the exerted torque reaches the target level. The rate of change in the EMG variable was calculated as the percentage ratio between the change in EMG estimate in one second and the initial value (expressed as %/s). The rate of changes in EMG estimates were used as indices of EMG manifestations of fatigue.

The COPD group was subdivided into a severe ($n = 5$) and a moderate ($n = 6$) COPD group (Table 1). Two-way ANOVA (muscle \times groups) followed by a t -test with Bonferroni correction were used to determine EMG differences between the 3 groups (severe COPD, moderate COPD, and healthy controls). FEV₁, FEV₁/FVC, BODE index, and 6MWT were analyzed using one-way ANOVA. The difference in subcutaneous tissue thickness between the whole COPD and healthy groups was analyzed using a t -test. The threshold for statistical significance was set at $p < 0.05$.

Results

All CV estimates were found to be within the physiological range (3.5 m/s to 5.7 m/s) and all EMG signals chosen for estimating the variables showed a high correlation coefficient (0.85 ± 0.5). Subcutaneous tissue thickness was greater in the COPD patients than in the healthy controls in both the VL (5.3 ± 1.2 mm in COPD patients vs. 3.5 ± 0.8 mm in controls; $p = 0.05$) and VM (5.9 ± 1.4 mm in COPD patients vs. 4.7 ± 1.1 mm in controls; $p = 0.05$). Due to this difference, the initial CV and MNF values could not be compared between the groups because the absolute value of these variables are strongly affected by subcutaneous tissue thickness (23).

Rate of change in CV

No significant muscle \times group interactions were found ($p = 0.542$) for the rate of change in CV. There was a main effect for group ($p < 0.001$) but not for muscle ($p = 0.390$). The decline in CV in the VL was steeper in the severe than in the moderate COPD patients (severe vs. moderate COPD $-0.47 \pm 0.08\%/s$, confidence interval [CI] 95% -0.69 to -0.25 , $p < 0.001$, $\eta^2 = 0.701$) and the healthy controls (severe COPD vs. controls $-0.45 \pm 0.07\%/s$, CI 95% -0.64 to -0.25 , $p < 0.001$, $\eta^2 = 0.685$) (Fig. 1). Similarly, the decline in CV in the VM was steeper in the severe than in the moderate COPD patients (severe vs. moderate COPD $-0.58 \pm 0.10\%/s$, CI 95% -0.86 to -0.31 , $p < 0.001$, $\eta^2 = 0.608$) and the healthy controls (severe COPD vs. controls $-0.54 \pm 0.09\%/s$, CI 95% -0.79 to -0.30 , $p < 0.001$, $\eta^2 = 0.583$). No significant difference in the rate of change in CV was found between the patients with moderate COPD and the healthy controls (Fig. 1).

Rate of change in MNF

No significant muscle \times group interactions were found ($p = 0.862$) for the rate of change in MNF. There was a main effect for group ($p = 0.010$) but not for muscle ($p = 0.666$). The decline in MNF in the VL was steeper in the severe than in the moderate COPD patients (severe vs. moderate COPD $-0.52 \pm 0.19\%/s$, CI 95% -1.02 to -0.17 , $p = 0.041$, $\eta^2 = 0.359$) and the healthy controls (severe COPD vs. controls $-0.53 \pm 0.17\%/s$, CI 95% -0.97 to -0.08 , $p = 0.018$, $\eta^2 = 0.385$). Similarly, the decline in MNF in the VM was steeper in the severe COPD patients than the healthy controls (severe COPD vs. controls $-0.60 \pm 0.20\%/s$, CI 95% -1.14 to -0.06 , $p = 0.026$, $\eta^2 = 0.342$). No significant difference in the rate of change in MNF was found between the severe and the moderate COPD patients (severe vs. moderate COPD $-0.60 \pm 0.23\%/s$, CI 95% -1.20 to 0.05 , $p = 0.053$, $\eta^2 = 0.265$) or between the moderate COPD patients and the healthy controls (Fig. 2).

Discussion

This is the first study that used CV to compare muscle qualities of COPD patients with those of age-matched healthy controls. The main finding of this study is that during fatiguing exercises of the legs, EMG fatigue appears earlier in severe COPD patients than in healthy controls. There was no difference in the pattern of EMG fatigue between the moderate COPD patients and controls (Fig. 1). A greater proportion of type II muscle

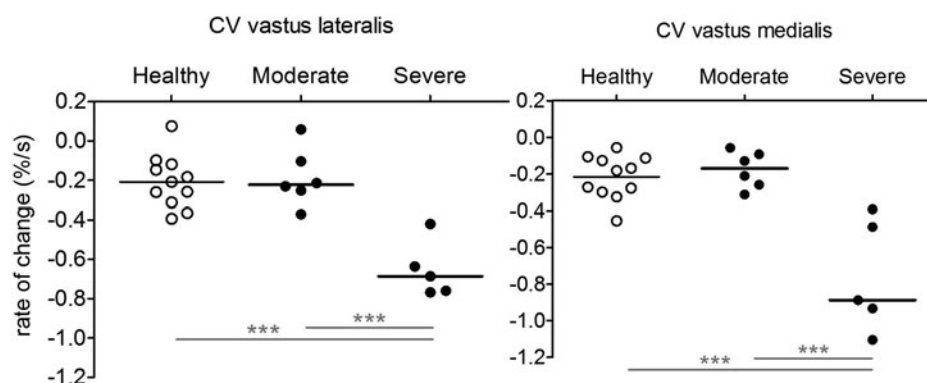


Figure 1. Scatter dot plot (and median) of rates of change (%/s) in muscle fiber conduction velocity (CV) during isometric contraction at 70% of maximal voluntary contraction of the vastus lateralis (left) and medialis (right) muscles. Statistically significant differences are reported: *** $p < 0.001$.

fibers has been demonstrated to generate greater EMG manifestations of fatigue, measured as a greater decrease in CV over time (13,14,24). These can be explained by the fact that type II muscle fibers rely on glycolytic processes and are more prone to fatigue than type I fibers (25), which relying on oxidative processes. Our results suggest that there may be a shift towards type II fibers in the muscles of severe COPD patients. These findings are supported by histochemical studies that showed a decrease in type I fibers, accompanied by an increase in type IIx fibers, in the muscles of severe COPD patients (1).

Protocols based on CV estimates, which were similar to the one we used, have been proposed as a potential tool for the non-invasive characterization of muscle fiber composition (15). Except a shift towards more glycolytic fibers, there are also other possible changes that may contribute to greater fatigability in patients with severe COPD (2). These include: a decreased capillary density, a reduction in capillary-muscle fiber contacts, and lower levels of oxidative enzyme activity (2). During exercise at the same absolute work rate, the blood pH decreases to lower levels in COPD patients than age-matched controls (26, 27). This phenomenon might be related to the greater CV reduction, identified in our study, in COPD patients compared to healthy controls.

Previous studies have reported that muscle dysfunction is present even in the early stages of COPD, indeed endurance capacity is impaired also in patients with mild to moderate disease (28, 29). The present results do not corroborate these findings, since augmented electromyographic fatigue was found only in patients with severe but not moderate COPD. Possibly,

not only muscles, but also more general factors would impair the endurance in the early stages of COPD.

Methodological approach

We adopted a protocol based on localized contractions (only a knee extension) in order to minimize the impact of muscle contractions on cardiopulmonary function (30). It seems that patients with severe ventilatory limitations (as those included in the present study) are able to keep a localized isometric contraction long enough in time to develop muscle fatigue.

Endurance performance of the quadriceps muscle has been lower in COPD patients than in healthy subjects, independent of the type of task and measurement technique (16). Although dynamic contractions may yield more information about fiber distribution than isometric contractions (31), we selected isometric contraction because it was the easiest to use. Moreover, we set a high contraction level to obtain fatigue quickly and to exclude motor unit rotation (i.e., motor units recruitment/de-recruitment) during the course of contraction, which can bias CV estimates (32). Another value of using high force levels is that fatigue will probably be less dependent on the central influence (changes in central activation); so the peripheral (muscular) fatigue will be expressed clearer (33).

In this study, with a high contraction level of 70% of MVC, the CV variable appeared to be more sensitive than the MNF in detecting differences in fatigue between the COPD patients and

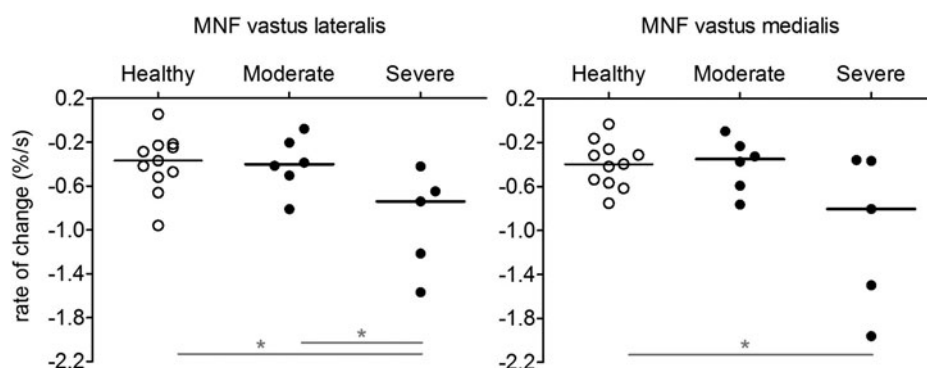


Figure 2. Scatter dot plot (and median) of rates of change (%/s) in mean power frequency (MNF) during isometric contraction at 70% of maximal voluntary contraction of the vastus lateralis (left) and medialis (right) muscles. Statistically significant differences are reported: * $p < 0.05$.

healthy subjects. Comparable results were found in our previous study (6). In contrast, two earlier studies, which only applied MNF, found differences in EMG fatigue between COPD patients and healthy controls only at low forces and not at higher forces (10% MVC versus 60% MVC) (30, 34). MNF is simpler to use because it only needs one-channel bipolar EMG whereas CV is obtained from multi-channel EMG (17). When fatigue protocols are used at high force levels, monitoring of CV seems more reliable and sensitive than spectral variables (such as MNF), because the latter are strongly affected by a number of confounding factors which less bias CV estimates (17).

Analysis of histochemical alterations induced by COPD have largely come from investigations on the VL muscle because it is readily accessible for biopsy and this has often been used to represent the whole quadriceps muscle. However, the VL is only one component of the quadriceps, and we found it useful to expand our knowledge and compare two components of the quadriceps, the VL and VM.

In healthy young and elderly men, the VL and VM differ in both histochemical (35) and EMG characteristics (36, 37). Nevertheless, in COPD patients, we found the same trends in the EMG indices of fatigue in both muscles.

Limitations

The main limitation of this study was the small sample size, which reduced the power of the results and the possibility to generalize our findings to the COPD population as a whole. Moreover, our sample was not balanced for the full spectrum of disease severity since we did not include patients with mild or very severe COPD. The isometric contraction we used for assessing fatigability is a highly reproducible task and is easy to perform; however, it is far unlike real-life movement or every day physical demands. Finally, because the results pertain to the VL and VM muscles, they cannot be extrapolated to other muscle groups that may have different usage and fatigue properties.

Conclusions

The rate of change in CV, as a sign of fatigue, during fatiguing quadriceps contraction was greater in the (male) patients with severe COPD than in the healthy, age-matched controls. No differences were found between the patients with moderate COPD and healthy controls. These findings may reflect a higher grade of reduction in muscle oxidative capacity, with a shift towards type II muscle fibers in severe COPD patients. Monitoring the rate of changes in CV during prolonged contractions may yield new insights in diseases compromising muscle qualities, such as COPD.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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